MILLENNIUM®

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30 July 2004

Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, Rm. 1061,
Rockville, MD 20852

Re: Critical Path Initiative [Docket No. 2004-N-0181, 69 *Federal Register*, 21839 – 21840, April 22, 2004]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc. ("Millennium"), a leading biopharmaceutical company based in Cambridge, Mass., co-promotes INTEGRILIN® (eptifibatide) Injection, a market-leading cardiovascular product, markets VELCADE™ (bortezomib) for Injection, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in three disease areas: cardiovascular, oncology and inflammation. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, Millennium is seeking to develop breakthrough personalized medicine products.

Millennium was intensely interested to review the Agency's recent report, *"Innovation/Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products"*. We agree strongly with FDA's analysis that current models for pharmaceutical development have to become markedly more efficient if the industry is to survive, and that FDA can play a critical role in facilitating translational research and the implementation of new approaches to regulatory development, review and approval. We warmly commend FDA for launching such a far-reaching initiative in this area, and we would like to support it with our comments and proposals for specific action, below.

1. Data Mining/ BioInformatics

   FDA mentions the vast quantities of data that it holds from many years' accumulation of regulatory submissions, and the possibility to mine these data for new information. We believe that, in aggregate, these data constitute a precious national resource that could yield much new and useful information about drugs and

their development – much of this information is not available to the industry and researchers. We support this approach despite the fact that most of the data currently held by FDA exist as records on paper. We know that technology exists for rapid scanning of paper records and building of specially- formatted data warehouses that facilitate indexing and intelligent mining of large datasets. It would seem that this project might fit well with the Agency's phased move to White Oak, and the associated opportunity to renew and upgrade its entire information infrastructure. In planning these new systems, we would encourage FDA to think boldly and imaginatively about future needs and possibilities, especially with regard to the following:

a. Sharing of study data among federal review and research agencies and the industry

Systems should be designed from the outset to enable easy access to the accumulated drug study data of all sponsors by staff at the three principal federal agencies involved in drug research and review – FDA, the National Institutes of Health (NIH) and the Centers for Medicare and Medicaid Services (CMS). The database should be structured and formatted in a uniform manner utilizing the XML backbone and Common Technical Document (CTD) conventions for clinical and non-clinical reports. All proprietary and personal identifiers should be removed. We believe that this will provide a powerful tool to enable truly evidence-based decision-making in convergent areas of health research, policy and regulation administered by these agencies. Large pooled sets of Safety data could enable companies and researchers determine if adverse events are due to a particular therapy or part of the disease process.

There will be legal and process issues entailed in implementing the full potential of this system, but we do not believe that any of them should present an insuperable obstacle to this important progress. One possible solution is the process used by the semi-conductor industry. Cooperation with the pharmaceutical industry should be sought to allow use of their submitted data in INDs, NDAs and BLAs in an anonymous format. An example of previous industry cooperation is the provision of placebo data and blood pressure measurements from their clinical trials of anti-hypertensive agents.

b. Voluntary submission of exploratory data

Previously, we have commended FDA for creating a pathway and an internal process for the voluntary submission of exploratory pharmacogenomic data[1]. We believe that this principle could profitably be extended to other types of exploratory data, but particularly data relating to the use of new technologies. These data should be accumulated and explored to find new relationships between different variables. They should also be used to allow FDA staff to become familiar with new technologies and their uses in drug development – we believe that this "training" aspect will become increasingly important.

[1] *Draft Guidance for Industry: Pharmacogenomic Data Submissions*, November, 2003.

2. Biomarkers

We agree with FDA that much of the impact of translational research on improving the efficiency of drug development could come through the development of new biomarkers. These could be developed through application of "classical" sciences, such as clinical pathology or toxicology, "new" sciences, such as pharmacogenomics and "new" technologies, such as imaging – or from the application of several approaches together. However, a key issue for sponsors will be to understand the contexts in which particular biomarkers will be considered to be "validated" or meaningful, especially for regulatory decision-making. We believe that the technical issues are of such complexity, but the potential benefits of such value, that FDA should establish a standing forum for the origination and coordination of initiatives in this regard, so as to prioritize the issues and study emergent biomarkers in a systematic way. In our view, this would add structure and focus to the current haphazard mixture of workshops, symposia and initiatives by scientific associations that do not have specific objectives in terms of regulatory science. Clearly, there would be many opportunities for collaborations with other agencies, academic groups and industry under this organization.

In this way, FDA should be prepared to enter into creative arrangements to assemble the raw data necessary to support the identification and validation of new biomarkers. An example might be the recruitment of syndicates of industrial and academic participants, who might agree to share their data with an independent organization that would conduct a meta-analysis and carry out any necessary supplementary research to provide a totality of evidence upon which to base a new biomarker.

FDA also should support the publication of all raw data from biomarker studies and have this information available in a proscribed format and grid for use by all researchers. This would be akin to access to the human genome data that were made publicly available. We also request active support from FDA for publishing all clinical trial results and data irrespective if the results were positive or negative.

3. Exploratory IND

The concept of providing a mechanism, by which sponsors would be able to open an Investigational New Drug application (IND) to conduct very circumscribed human studies carrying minimal risk on the basis of a reduced data burden is strongly endorsed. We are aware that FDA is currently considering guidance to establish such a process. In so doing, we believe that there is scope for the Agency to be relatively aggressive in seeking to reduce the quantity and types of data that sponsors must submit, and the drug quality standards that they must observe, in order to justify many exploratory investigations. This is not to argue for a cavalier attitude to experimental safety, which we believe is paramount, but we believe that many restricted but informative early investigations could be carried out safely without much of the data that is required to be submitted in a normal IND, and should specifically address laboratory-scale Good Manufacturing Practices (GMP). These requirements often do not add to the safety of the procedures, but do add significantly to the costs and complexity of conducting exploratory studies. This is especially relevant in the new era of breakthrough products that affect new pathways or mechanisms of disease. It is

essential to evaluate the effects in humans since animal models may not be available or validated. Implementing studies to evaluate the effects on various pathways and target organs would differ from traditional dose range toxicity studies typically done under an IND. With new imaging techniques, effects at the target site can be evaluated. Accessing these types of data rapidly and efficiently can help navigate researchers in the right direction and allow rapid termination of clinical development if the purported effects are not seen in humans. For such studies, the amount of non-clinical toxicology data required should be re-evaluated. The laboratory scale GMP requirements should be defined since many exploratory studies would include the use of 'challenge' tests, biomarkers and ligands. Also, a possible "DMF catalog" could be developed for cross-referencing for the use of challenge molecules, ligands, etc. The main idea behind an exploratory IND would be 'flexibility' to do early clinical research and incorporate concepts of study design including modeling and use of nanotechnology and 'nano' doses of potential therapeutic molecules.

4. Regulatory Guidance

It is critical that the FDA continue to define the clinical efficacy endpoints for achieving approval. Vetting these endpoints through public forums and Advisory Committees is essential so that once the studies are done there would be no 'second-guessing' by Advisory Committee members after the studies are completed. Negative votes by Advisory Committees on drug approval study endpoints in the past have been problematic for FDA and the industry particularly when the Agency and the company had agreed on study design.

In reviewing FDA's list of regulatory guidances, and the Agency's guidance agenda for FY2004, we note some absences of guidances that could contribute significantly to expediting drug development. It would be very helpful if the Agency would prioritize these for publication at an early date.

a. Draft guidance on exploratory INDs – see Item 3 above. We understand that the Agency is already working on this, and we await publication of draft guidance with great interest.

b. Draft guidance on the use of Bayesian approaches in clinical trials – FDA recently cosponsored a workshop on this topic, and we suggest that the learnings from this event should be translated into a draft guidance as soon as possible. Bayesian approaches could help to improve the efficiency and timeliness of many types of clinical studies and, in conjunction with classical frequentist methods, could be an important addition to the regulatory armamentarium.

c. International Conference on Harmonization (ICH) Guidance on Reporting Pharmacogenomic Studies – FDA issued important draft guidance on pharmacogenomic data submissions in 2003. Other international regulatory agencies (EU, Japan) are also putting in place equivalent processes for their jurisdictions. We do not believe that it is necessary or appropriate to try to harmonize most aspects of these processes at the present time. However, we do see a need to obtain agreement between regulatory authorities on the

content and format of pharmacogenomic study reports. We see this as essentially a specialized subset of the Common Technical Document, so it would be appropriate to consider at the ICH level. More importantly, we believe that it would promote the incorporation of pharmacogenomics into drug development, and avoid inefficiencies arising from different national requirements, if it was clear what information should be included in reports of pharmacogenomic studies for global submission, and how the information should be formatted.

d. Combination guidelines should be developed addressing use and evaluation of two, three or more compounds developed for use in combination where any of the compounds alone may not be effective. This may become more likely with new research into disease targets and various pathways that may be affected.

5. Imaging
The FDA should fully support efforts related to 'real time' in vivo imaging in humans and work closely with other agencies such as the NIH and NCI in validating these techniques and establishing criteria for their use as efficacy endpoints in evaluating drug therapy. One such example would be 3D imaging of tumors rather than reliance on current RECIST criteria for tumor shrinkage.

6. Toxicogenomics
FDA should evaluate new methods of detecting toxicity by evaluating the potential of toxicogenomics in animal models and its relevance to human disease and toxicity prediction.

7. The Process Analytical technology (PAT) This FDA-initiated approach to manufacturing should be continued and enhanced to continue efforts in risk-based approaches to more efficient manufacturing of medicinal products.

We appreciate the opportunity to comment on this important report and look forward to working with FDA to realize its potential.

Sincerely,

Robert G. Pietrusko, Pharm.D.,
Senior Vice-President, Worldwide Regulatory Affairs and Pharmacovigilance,
Millennium Pharmaceuticals, Inc